UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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JAN 18 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: SC-0224

TO: Robert Taylor, PM #25
Herbicides-Fungicides Branch
Registration Division (TS-767)

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch (TS-769)

FROM: Roland A. Gessert, DVM
Review Section #1
Toxicology Branch/HED (TS-769)

Roland A. Gessert 1/12/84

1/17/84

Applicant: Stauffer Chemical Company

Mr. Jack Wise, Manager, Regulatory Relations, Stauffer Chemical Company, wrote to confirm his meeting on September 1, 1983 with William Burnam and Bruce Jaeger concerning termination of the 2-year mouse study on SC-0224 which was started in July 1982.

Stauffer started an 18-month mouse study in accordance with EPA guidelines in April 1982.

Toxicology Branch acknowledges this information and looks forward to receipt of the complete data package.

TS-769:GESSERT:sll:X73710:1/11/84: card 6

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Reviewed by: William Dykstra
Section II, Toxicology Branch (TS-769C)
Secondary reviewer: Edwin Budd
Section II, Toxicology Branch (TS-769C)

DATA EVALUATION REPORT

Study Type: 83-5, Chronic Toxicity/Oncogenicity

TOX Chem No.: 893C
MRID No.: None

Accession Number: 402140-07 (Vol. 1-7)

Test Material: Sulfosate

Synonyms: SC-0224

Study Number: T-11082

Sponsor: Stauffer Chemical Company

Testing Facility: Stauffer Laboratory
Farmington, CT

Title of Report: Two-Year Chronic Toxicity and Oncogenicity Dietary Study with SC-0224 in Rats

Authors: Pavkov, K.L.; Wyand, S.

Report Issued: April 3, 1987

Conclusions: [Tentative]

The oncogenic potential was negative at the highest dose tested (HDT) of 1000 ppm. The NOEL for systemic toxicity is 100 ppm. At the LEL of 500 ppm, lactate dehydrogenase levels in male and female rats at 6 and 12 months were decreased in a dose-related manner.

At 1000 ppm there were decreased body weights for males (8 to 10%) for the first 49 weeks of the study and decreased body weights for females (8 to 9%) for the first 75 weeks of the study. The body weight decreases for 1000 ppm (HDT) male and female rats are considered sufficient evidence that an MTD was reached in this study.

Histologically, at 1000 ppm, there was an increased incidence of chronic inflammation of the larynx and nasopharynx in male rats.

Classification: Core-Supplementary, because the tissue masses listed in Appendix I (clinical observations) and Appendix L (necropsy observations) were not clearly

2

identified in the histopathology sheets (Appendix N) as being histologically examined. This deficiency has to be resolved by the registrant.

Special Review Criteria (40 CFR 154.7): N/A

3

REVIEW

I. Two-Year Chronic Toxicity and Oncogenicity Study With SC-0224 in Rats (Stauffer Labs Report No. T-11082; April 3, 1987).

Test Material: Technical SC-0224 (Trimethylsulfonium carboxymethyl-aminomethylphosphonate, active ingredient); Lot No. WRC 8108-24-1, EHC Code No. EHC 0469-15. Clear aqueous solution, 56.2% active ingredient (ai) on a w/w basis.

Experimental Design:

Randomized groups of male and female Charles River (Kensington, New York) Sprague-Dawley-derived rats (Crl:CD[SD]BR) were used in the study. The rats were identified by an ear tag and were housed individually.

The test material was administered continuously in the diet (Purina Certified Rodent Chow Meal 5002) for 24 months. The experimental design is shown below.

		Number of Animals	
Dose Group	ppm ai	Male	Female
0	Control[a]	60	60
1	0[b]	80	80
2	100	80	80
3	500	80	80
4	1000	90	90

[a]Basal diet, no vehicle.
[b]Basal diet plus vehicle (propylene glycol at 1% w/w).

There were interim sacrifices of variable numbers of rats at 6, 12, and 18 months. The number of rats scheduled for the full 24-month study duration was 50/sex/group.

Rats were observed twice daily for toxic signs. A general physical examination was performed on all animals once per week including palpatation for nodules or tissue masses. Moribund rats were sacrificed to avoid tissue autolysis.

Individual body weights were recorded weekly for the first 13 weeks of the study and every other week thereafter. Body weights at the time of necropsy were recorded for animals sacrificed at 6, 12, or 18 months and at study termination. Individual food consumption was measured

weekly during the first 13 weeks of the study and on alternate weeks thereafter by determining the sum of allocated feed for a 7-day interval minus the residual from the 7-day period. Feed efficiency was calculated at each interval.

Blood samples were drawn for hematologic analyses (listed below) from 20 fasted animals of each sex during the quarantine-acclimation period and from 20 in each dose group and vehicle control (0 ppm) at 3, 6, 12, 18, and 24 months (the control basal diet group was evaluated only at 12 and 24 months). As much as possible, the same rats were sampled at each time interval.

Hematology parameters evaluated included:

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Erythrocyte count (RBC)
- Total leukocyte count (WBC)
- Differential leukocyte count (also prior to termination of any animal)
  - Immature neutrophils (Bands)
  - Mature neutrophils (Segs)
  - Lymphocytes (Lymph)
  - Monocytes (Mono)
  - Basophils (Baso)
  - Eosinophils (Eos)
- Platelet count (PLT)
- Prothrombin time (PT) (10/sex/dose at termination)
- Partial thromboplastin time (PTT) (10 sex/dose at termination)

Samples for blood chemistry were obtained from 10 fasted rats/sex/dose group (same animals used for hematologic analyses) at 6, 12, 18, and 24 months. The blood chemistry parameters evaluated are listed below. When sample volume was insufficient, those parameters of the highest priority were measured in the following order:

- Asparate aminotransferase (SGOT)
- Alanine aminotransaminase (SGPT)
- Gamma glutamyl transferase (GGT)
- Alkaline phosphatase (Alk. Phos.)
- Total protein (T. Prot.)
- Total bilirubin (T. Bili.)
- Albumin (Alb)
- Globulin
- Blood urea nitrogen (BUN)
- Glucose (Glu)
- Sodium (Na)

5

Calcium (Ca)
Potassium (K)
Inorganic phosphorus (Phos)
Chloride (Cl)
Creatinine (Creat)
Cholesterol (Choles)
Triglycerides (Triglyc)
Creatinine phosphokinase (CPK)
Lactate dehydrogenase (LDH)
Plasma cholinesterase (P ChE)
Red blood cell cholinesterase (RBC ChE)
A/G ratio
Uric acid
Protein electrophoresis

The right or left half of the brain from five rats/sex/dose level was homogenized at 6, 12, 18, and 24 months to measure the cholinesterase activity per gram of protein (determined by the Lowry method).

Urinalyses were performed for 20 fasted rats/sex/dose level (same animals mentioned above in hematology). The parameters evaluated included:

Appearance
Microscopic examination of sediment
Specific gravity (SpGr)
pH
Protein (Prot)
Glucose (Glu)
Ketones (Ket)
Occult blood (Occ Bl)
Urobilinogen (U-blin)
Bilirubin (Bili)

All rats were necropsied by trained prosectors under the direction of a veterinary pathologist. The animals were anesthetized by injecting saline-diluted sodium pentobarbital IP and exsanguinated by severing the abdominal aorta and vena cava. They were examined for external abnormalities, including palpable masses. Viscera and body cavities were also examined.

The sacrifice schedule is shown below.

		Sacrifice Interval (Months)			
Group	ppm	6	12	18	24
0	Control	--	20(1)	--	Survivors

(1) 10/sex/group

Group	ppm	Sacrifice Interval (Months) 6	12	18	24
1	0	20(1)	20	20(1)	Survivors
2	100	20	20	20	Survivors
3	500	20	20	20	Survivors
4	1000	20	40(2)	20	Survivors

(1) 10/sex/group.
(2) 20/sex/group.

The following tissues were fixed in 10% neutral buffered formalin or 2.5% buffered glutaraldehyde (BG):

Skin
Mammary gland
Muscle-thigh
Tibiofemoral joint
Sternum
*Lungs
*Heart
Aorta - ascending and thoracic
*Spleen
Thymus
Bone marrow - Sternal
Lymph nodes - mesenteric and mediastinal
Salivary glands - partotid and mandibular
Buccal/alveolar mucosa
Tongue
Esophagus
Stomach
Duodenum
Jejunum
Ileum

Cecum
Colon
Rectum
Pancreas
*Liver
*Kidneys

Nasal passage
Paranasal sinus
Nasopharynx
Larynx
Trachea
Urinary bladder
*Testes (BG)
Epididymides (BG)
Prostate
Seminal vesicles
Coagulating glands
*Ovaries (BG)
Vagina
Cervix
*Uterus
*Pituitary (BG)
Thyroids
Parathyroids
*Adrenals (BG)
*Brain
Spinal cord - cervical, thoracic and lumbar
Sciatic nerve
Eyes (BG)
Harderian glands (BG)
Zymbal's glands

Middle ear(s)
Gross lesions (as specified by the pathologist)

Those organs marked (*) above were weighed for rats sacrificed at the interim and final terminations. The

paired organs were weighed together for the 6-month interim sacrifice but were weighed separately thereafter. All tissues on the above list were routinely processed for light microscopic examination for all animals.

Statistical Analysis

Continuous data were analyzed using a one-way analysis of variance (ANOVA; Winer, 1962) and Dunnett's Test (Dunnett, 1964) to compare test groups with controls. Test group data were compared to the 0-ppm (Control) dose groups at 3, 6, and 18 months and were compared to the basal diet (Control) groups at 12 and 24 months. The criterion for statistical significance was $p < 0.05$. Values of $p < 0.01$ were also indicated. The statistical significance was not determined at the $p < 0.001$ level because all Dunnetts' tables only include 0.05 and 0.01 values.

Results:

In the initial 2 to 3 weeks, mean body weights of male and female rats were statistically significantly decreased in all test groups in comparison to the respective control groups. These decreases ranged from 4.4 to 8.3 percent for males and 2.7 to 3.7 percent for females.

Mean body weights of the 1000 ppm dose groups for both males and females remained significantly lower through 49 weeks (males) and through 75 weeks (females). These decreases ranged from 8.3 to 10.1 percent for males during this period (49 weeks) and from 8.2 to 9.4 percent for females during this period (75 weeks).

At 24 months, absolute weight gain was comparable for both males and females of all groups in comparison to week 0 of the study. Males showed mean increases of 457, 507, 403, 406, and 473 g for groups control, 0, 100, 500, and 1000 ppm, respectively. Females showed mean increases of 234, 231, 314, 266, and 244 g for groups control, 0, 100, 500, and 1000 ppm, respectively.

The body weight decreases for high-dose male and female rats during the study are considered sufficient evidence that an MTD was reached in the study.

The average concentrations of SC-0224 active ingredient (measured by separate anion and cation analyses) were within 15 percent (anion analysis) and 18 percent (cation analysis) of the nominal values measured at regular intervals during the study.

8

The calculated intake of active ingredient on a mg/kg/day basis is shown below:

Nominal ppm ai	Males	Females
100	4.2	5.4
500	21.2	27.0
1000	41.8	55.7

Food consumption of male and female rats at 1000 ppm was occasionally decreased during the study in comparison to control levels. The decreased food consumption was not considered responsible for the decreased body weights of male and female rats at 1000 ppm observed during the study.

Feed efficiency was comparable for males and females between controls and treated groups during the study.

There were no compound-related effects on survival for male and female rats during the study. At study termination (weeks 105 or 106), the number of survivors in each group of males was 17, 18, 12, 19, and 23 for control, 0, 100, 500, and 1000 ppm, respectively. For each group of females at study termination (weeks 105 or 106), the number of survivors was 16, 15, 25, 15 and 16 for control, 0, 100, 500, and 1000 ppm, respectively.

There were no compound-related clinical signs, including the onset, number, and location of palpable masses, for both male and female rats during the study. The most common observations were abrasions, anorexia, alopecia, broken teeth, chromodacryorrhea, chromorhinorrhea, dehydration, emaciation, exophthalmus, hair loss, hematuria, loose stool, malocclusion, pallor, rough/wet hair coat, swollen or torn ears, and scabs.

Ophthalmoscopic examinations at 6, 12, 18, and 24 months did not show any compound-related effects. The most common observation was conjunctivitis and was unrelated to treatment.

Evaluation of hematological data showed that at 3 months, the leukocyte counts (WBC) for the males of the 500 and 1000 ppm dose group and the females of the 1000 ppm dose group were reduced to 85.6, 85.6, and 84 percent of the respective 0 ppm dose group values. These changes are shown below.

9

Leukocytes ($10^3/mm^3$)

	Males	3 Months	Females
Control	---	Mean + S.D.	---
0	13.2 ± 2.7		9.4 ± 2.8
100	11.9 ± 1.3		8.2 ± 2.4
500	11.3* ± 2.5		8.6 ± 2.0
1000	11.3* ± 2.4		7.9 ± 2.6

*$p < 0.05$

Evaluation of individual leukocyte data for male rats at 3 months showed a 0 ppm mean of 13.2 ± 2.7 $10^3/mm^3$ and a range of 8.3 to 21.3 $10^3/mm^3$.

In comparison, values at 500 ppm had a mean of 11.3 ± 2.5 $10^3/mm^3$ and a range of 8.5 to 16.8 $10^3/mm^3$, whereas values at 1000 ppm had a mean of 11.3 ± 2.4 $10^3/mm^3$ with a range of 7.6 to 15.0 $10^3/mm^3$.

The decrease in mean leukocyte values for males at 500 and 1000 ppm are not considered toxicologically significant since (1) mean values ± SD were within control mean ± SD values; (2) individual values ranged generally within the control range; and (3) the transient response at 3 months was not observed at 6, 12, 18, or 24 months as a dose-related finding.

Similarly, evaluation of individual leukocyte data for female rats at 3 months showed that the values for 0 ppm ranged from 5.4 to 12.5 (with animal number 1090 showing 17.5) $10^3/mm^3$. At 1000 ppm, the range was 4.0 to 14.3 $10^3/mm^3$. It can be seen that the individual values at 1000 ppm ranged generally within the control values with the exception of the single high value value of 17.5 $10^3/mm^3$ for animal #1090. Also, as with male rats, the mean values ± SD were within control mean ± SD and the finding did appear in a dose-related manner at 6, 12, 18, and 24 months.

At 12 months, decreases in mean hemoglobin and hematocrit values of females at 100 ppm were statistically significantly different in comparison to control values but were not considered toxicologically significant since they were not dose-related.

At 6 months, the activated partial thromboplastin times (PTT) for female rats in the 1000 ppm group were statistically significantly decreased ($p < 0.05$) in comparison to controls. At 1000 ppm, the mean value was 13 ± 1 seconds compared to 15 ± 2 seconds in the control.

10

Individual control values ranged from 13 to 18 seconds in comparison to the values at 1000 ppm which ranged from 11 to 14 seconds. These slight effects were not considered toxicologically significant.

At 12 months, the PTT times for female rats at 0, 100, and 500 ppm (but not 1000 ppm) were statistically significantly decreased ($p < 0.05$) in comparison to controls (79 to 89% of the control values). The mean values at 0, 100, and 500 ppm were 16 ± 1, 15 ± 1, and 17 ± 1, respectively, in comparison to the control value which was 19 ± 1. Individual values at 0, 100, and 500 ppm ranged between 15 and 16, 14 and 17, and 15 and 19, respectively, in comparison to the control range which was 17 to 20. These slight effects were not considered toxicologically significant.

All other hematological parameters for males and females were comparable to control values for all groups and for each time interval (3, 6, 12, 18, and 24 months).

The following serum enzyme parameters showed comparable values between control and treated groups of both sexes: AST/SGOT, ALT/SGPT, GGT, SAP, albumin, glucose, calcium, phosphorus, and sodium.

Lactate dehydrogenase levels (IU/L) showed statistically significant decreases at 6 and 12 months as shown on page 13.

The decreases in males and females at 6 and 12 months are in a dose-related manner and are statistically significant. These findings are considered clinically significant and may be indicative of progressive systemic toxicity related to treatment. The NOEL for this effect is 100 ppm.

Statistically significant decreases in creatine phosphokinase values (IU/L) at 1000 ppm in males and females at 6 months were not considered toxicologically significant. Creatine phosphokinase data are shown on page 14.

With respect to total bilirubin, the statistically significantly decreased values for females at 0, 100, 500, and 1000 ppm at 12 months and 500 ppm at 18 months, are within the range of control values. Control values ranged from 0.2 to 1.1 mg/dl at 12 months and 0.1 to 0.4 mg/dl at 18 months. Therefore, the decreased values observed do not indicate toxicological significance. Total bilirubin values are shown on page 15.

Mean values for BUN (mg/dl) show decreased values for females at 500 and 1000 ppm at 6 months and also at 1000 ppm at 18 months. As shown with other serum chemistries, most of the decreased values are within the range of 0 ppm values for females. Therefore, the decreased values in the treated groups are not considered toxicologically significant. BUN values are presented on page 16.

Mean values for creatinine show statistically significant decreases at 12 months in females at 0, 100, 500, and 1000 ppm. Control values for creatinine in females at 12 months range between 0.5 and 1.9 mg/dl and encompass the range of values for the females at 0 ppm (0.7 to 1.0 mg/dl), 100 ppm (0.6 to 1.0 mg/dl), 500 ppm (0.6 to 0.8 mg/dl) and 1000 ppm (0.6 to 0.90 mg/dl). Therefore, the decreased mean values are not considered toxicologically significant. Creatinine values for the study are shown on page 17.

The mean value for uric acid in females at 12 months at 1000 ppm was statistically significantly decreased in comparison to the control values. At 1000 ppm, the values ranged from 0.2 to 1.0 mg/dl, whereas the control values at 12 months for females ranged from 0.8 to 1.9 mg/dl.

Although the range of uric acid values at 1000 ppm is less than the range of control values, the transient decrease at only 12 months (which was not either dose-related at that time or was extended into 18 or 24 months) is not considered toxicologically significant. Uric acid acid data are presented on page 18.

Cholesterol mean values were significantly decreased in 1000 ppm males at 6 months and in 500 and 1000 ppm females at 18 months. Male 0 ppm values at 6 months ranged between 60 and 115 mg/dl in comparison to the range of 53 to 77 mg/dl values for males at 1000 ppm.

The decreases at the 1000 ppm level in males at 6 months are not considered clinically significant in comparison to 0 ppm values. For females at 18 months, 0 ppm values for cholesterol ranged from 71 to 121 mg/dl. In comparison to this, the range of female values at 500 ppm were 49 to 123 mg/dl and at 1000 ppm were 50 to 96 mg/dl. The statistically significant decreases at 18 months in females are not considered clinically significant. The data for cholesterol values for the study are shown on page 19.

Decreased triglycerides were observed to be significantly decreased at 12 months in 100 and 1000 ppm females and at 18 months in 1000 ppm females.

Control values for females at 12 months ranged from 50 to 804 mg/dl, with a mean and S.D. of 410 ± 254 mg/dl. It should be noted that female control rat #942 had a 50 mg/dl value for triglyceride whereas the next lowest value in control females was 206 mg/dl for female rat #945. The decreased values of female rats at 12 months in the 100 and 1000 ppm groups ranged from 70 to 526 mg/dl and 30 to 332 mg/dl, respectively. Therefore, the range of control values for triglycerides, although higher than all groups including 0 ppm, essentially encompasses the range of decreased values observed in females at 100 and 1000 ppm. These decreased values at 100 and 1000 ppm are not considered toxicologically significant.

Similarly, at 18 months, the 0 ppm range for females is 30 to 405 mg/dl, with a mean and S.D. of 212 ± 147 mg/dl. The range of values in females at 1000 ppm is 33 to 225 mg/dl, with a mean S.D. of 94 ± 63 mg/dl. The decreased values observed in females at 1000 ppm are within the range of 0 ppm values observed and are not considered toxicologically significant. The study data for serum triglycerides are shown on page 20.

Mean and S.D. values for total protein and globulin were increased in a dose-related fashion at 12 months only in treated females. Additionally, the values were statistically significantly increased for both total protein and globulin at 500 and 1000 ppm ($p < 0.05$ and $p < 0.01$, respectively).

The data for total protein and globulin are presented on pages 22 and 23 as obtained from the report.

It can be seen from the above-mentioned tables that the mean total protein and globulin values for females at 12 months at control and 0 ppm levels are within the range of control and 0 ppm values at other (6, 18, and 24 months) sampling intervals. Additionally, the increases observed at 500 and 1000 ppm at 12 months exceed the mean values for the 500 and 1000 ppm levels at other sampling intervals (6, 18, and 24 months).

13

Summary of Serum Lactate Dehydrogenase (IU/L) Mean Values for Rats Given SC-0224 in Diet

	Dosage Group (ppm)	Pretest n = 20	6 Months n = 10	12 Months n = 10	18 Months n = 10	24 Months n = 10
Males	Control	402 (221)		488 (206)		861 (442)[a]
	0		591 (246)	368 (174)	483 (226)	883 (286)[a]
	100		616 (237)	308 (234)	768 (392)	836 (307)[a]
	500		337 (154)*	206 (113)*	311 (185)	892 (409)
	1000		248 (180)**	138 (80)**	567 (341)	933 (326)
Females	Control	607 (397)		509 (286)		1086 (330)
	0		536 (126)	453 (288)	492 (268)	1032 (491)[b]
	100		481 (152)	503 (326)	419 (204)	881 (473)
	500		323 (173)**	387 (225)	698 (366)	973 (308)
	1000		160 (75)**	196 (114)	401 (305)	867 (258)[c]

* Significantly different from control; $p < 0.05$
** Significantly different from control; $p < 0.01$
() Standard deviation
a n = 9
b n = 7
c n = 8

Summary of Serum Creatine Phosphokinase (IU/L) Mean Values for Rats Given SC-0224 in Diet

	Dosage Group (ppm)	Pretest n = 20	6 Months n = 10	12 Months n = 10	18 Months n = 10	24 Months n = 10
Males	Control	359 (400)		152 (18)		155 (59)[a]
	0		213 (72)	109 (75)	200 (80)	179 (60)[a]
	100		260 (118)	73 (43)	306 (143)	177 (76)[a]
	500		149 (97)[a]	82 (37)	158 (155)	233 (102)
	1000		114 (43)*	66 (45)	219 (135)	226 (62)[a]
Females	Control	388 (208)		129 (69)		326 (102)
	0		168 (62)	111 (42)	264 (273)	294 (118)[b]
	100		192 (66)	113 (63)	205 (116)	266 (174)
	500		118 (50)	89 (64)	232 (121)	295 (81)
	1000		95 (43)*	96 (59)	235 (169)	307 (136)[c]

* Significantly different from control; $p < 0.05$
** Significantly different from control; $p < 0.01$
() Standard deviation
a n = 9
b n = 7
c n = 8

Summary of Serum Total Bilirubin (mg/dl) Mean Values for Rats Given SC-0224 in Diet

	Dosage Group (ppm)	Pretest n = 20	6 Months n = 10	12 Months n = 10	18 Months n = 10	24 Months n = 10
Males	Control	0.2 (0.1)		0.3 (0.1)		0.2 (0.1)[a]
	0		0.3 (0.1)	0.3 (< 0.1)	0.2 (0.1)	0.1 (0.1)[a]
	100		0.2 (0.1)	0.3 (0.1)	0.2 (0.1)	0.1 (0.1)[a]
	500		0.3 (0.1)[a]	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
	1000		0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.0)
Females	Control	0.2 (0.1)		0.5 (0.3)		0.3 (0.2)
	0		0.2 (< 0.1)	0.3 (0.1)*	0.3 (0.1)	0.2 (0.1)[b]
	100		0.2 (0.0)	0.3 (0.1)*	0.2 (0.1)	0.3 (0.3)
	500		0.2 (< 0.1)	0.4 (0.2)*	0.2 (0.1)*	0.2 (0.2)
	1000		0.2 (0.1)	0.3 (0.1)**	0.2 (0.0)	0.2 (0.1)[c]

* Significantly different from control; $p < 0.05$
** Significantly different from control; $p < 0.01$
() Standard deviation
a n = 9
b n = 7
c n = 8

Summary of Serum Blood Urea Nitrogen (mg/dl) Mean Values for Rats Given SC-0224 in Diet

	Dosage Group (ppm)	Pretest n = 20	6 Months n = 10	12 Months n = 10	18 Months n = 10	24 Months n = 10
Males	Control	14 (2)		16 (2)		24 (16)[a]
	0		15 (2)	15 (4)	21 (18)	22 (13)[a]
	100		14 (2)	14 (3)	16 (4)	20 (4)[a]
	500		15 (2)	15 (2)	20 (12)	22 (11)
	1000		15 (3)	14 (3)	16 (5)	24 (15)
Females	Control	17 (3)		14 (2)		13 (5)
	0		20 (2)	15 (2)	14 (2)	14 (5)[b]
	100		18 (2)	15 (4)	14 (3)	15 (4)
	500		17 (1)*	15 (3)	13 (2)	13 (4)
	1000		18 (4)*	14 (3)	11 (2)*	15 (5)[c]

* Significantly different from control; $p < 0.05$
** Significantly different from control; $p < 0.01$
() Standard deviation
a n = 9
b n = 7
c n = 8

Summary of Serum Creatinine (mg/dl) Mean Values for Rats Given SC-0224 in Diet

	Dosage Group (ppm)	Pretest n = 20	6 Months n = 10	12 Months n = 10	18 Months n = 10	24 Months n = 10
Males	Control	0.7 (0.1)		0.8 (0.1)		1.1 (0.8)[a]
	0		0.8 (0.1)	0.7 (0.1)	1.1 (0.9)	0.9 (0.4)[a]
	100		0.8 (0.2)	0.7 (0.1)	0.9 (0.2)	0.8 (0.1)[a]
	500		0.8 (0.1)[a]	0.8 (0.1)	1.0 (0.6)	0.8 (0.3)
	1000		0.8 (0.1)	0.7 (0.1)	0.8 (0.1)	1.0 (0.5)
Females	Control	0.2 (0.1)		1.0 (0.4)		0.6 (0.1)
	0		0.8 (0.1)	0.7 (0.1)*	0.7 (0.1)	0.7 (0.2)[b]
	100		0.8 (< 0.1)[a]	0.8 (0.1)*	0.8 (0.1)	0.6 (0.1)
	500		0.7 (0.1)	0.7 (0.1)*	0.7 (0.1)	0.6 (0.1)
	1000		0.7 (0.1)	0.7 (0.1)**	0.7 (0.1)	0.6 (0.1)[c]

* Significantly different from control; $p < 0.05$
** Significantly different from control; $p < 0.01$
() Standard deviation
[a] n = 9
[b] n = 7
[c] n = 8

Summary of Serum Uric Acid (mg/dl) Mean Values for Rats Given SC-0224 in Diet

	Dosage Group (ppm)	6 Months n = 10	12 Months n = 10	18 Months n = 10	24 Months n = 10
Males	Control		1.6 (0.7)		1.7 (0.4)[a]
	0	2.1 (0.4)	1.1 (0.3)	2.2 (1.6)	1.4 (0.2)[a]
	100	1.8 (0.3)[a]	1.1 (0.4)	1.3 (0.6)	1.8 (0.4)[a]
	500	1.4 (0.7)[b]	1.4 (0.5)	1.4 (0.6)	1.3 (0.6)
	1000	1.9 (0.8)	1.0 (0.4)	1.3 (1.2)	1.4 (0.7)
Females	Control		1.1 (0.3)		1.5 (0.4)
	0	1.3 (0.7)[b]	0.9 (0.3)	1.5 (0.7)	1.4 (0.5)[b]
	100	0.9 (0.6)[b]	0.8 (0.3)	1.2 (0.5)[b]	1.3 (0.5)
	500	1.1 (0.4)[a]	0.9 (0.5)	1.0 (0.4)	1.2 (0.4)
	1000	0.8 (0.2)	0.5 (0.3)*	1.0 (0.4)[b]	1.0 (0.3)[a]

* Significantly different from control; $p < 0.05$
** Significantly different from control; $p < 0.01$
() Standard deviation
a n = 9
b n = 7
c n = 8

Summary of Serum Cholesterol (mg/dl) Mean Values for Rats Given SC-0224 in Diet

	Dosage Group (ppm)	Pretest n = 20	6 Months n = 10	12 Months n = 10	18 Months n = 10	24 Months n = 10
Males	Control	40 (11)		114 (55)		102 (40)[a]
	0		78 (18)	102 (36)	139 (80)	98 (40)[a]
	100		78 (17)	107 (36)	123 (143)	114 (43)[a]
	500		80 (15)[a]	99 (36)	125 (155)	136 (72)
	1000		61 (8)*	76 (18)	94 (135)	117 (44)
Females	Control	51 (13)		91 (26)		106 (49)
	0		77 (11)	84 (9)	100 (20)	95 (21)[b]
	100		69 (20)[a]	84 (35)	82 (16)	95 (54)
	500		71 (13)[a]	67 (19)	74 (23)*	79 (28)
	1000		81 (27)*	74 (25)	76 (15)*	68 (29)[c]

* Significantly different from control; $p < 0.05$
** Significantly different from control; $p < 0.01$
() Standard deviation
a n = 9
b n = 7
c n = 8

Summary of Serum Triglycerides (mg/dl) Mean Values for Rats Given SC-0224 in Diet

	Dosage Group (ppm)	Pretest n = 20	6 Months n = 10	12 Months n = 10	18 Months n = 10	24 Months n = 10
Males	Control			224 (81)		155 (95)[b]
	0		201 (144)	298 (123)	191 (78)	95 (68)[b]
	100		188 (87)	264 (194)	169 (93)[b]	97 (48)[b]
	500		173 (59)	238 (89)	145 (72)	151 (96)
	1000		128 (55)	217 (98)	128 (83)	111 (47)[b]
Females	Control			410 (254)		161 (154)
	0		42 (12)	243 (99)	212 (147)	135 (83)[c]
	100		70 (59)[b]	215 (139)*	135 (88)	219 (302)
	500		71 (40)	242 (116)	106 (69)	128 (175)
	1000		52 (47)	154 (110)**	94 (63)*	97 (77)[d]

* Significantly different from control; $p < 0.05$
** Significantly different from control; $p < 0.01$
() Standard deviation
a Test not performed due to problem with reagent subsystem and insufficient sample for rerun.
b n = 9
c n = 7
d n = 8

Although these findings tend to support the conclusion that the increased total protein and globulin values observed in females at 12 months at 500 and 1000 ppm are toxicologically significant, other pathological findings could not be correlated with these clinical chemistry findings. Specifically, there were no toxic signs or organ weight changes, including liver and kidney, for females at 12 months or at any other sampling interval. Additionally, there were no histopathological lesions in females which could be correlated with the clinical pathology data.

Since the increase in total protein and globulin did not occur at other sampling intervals during the study, the results at 12 months are not considered toxicologically significant. The increase in total protein and globulin at 12 months is not considered an effect.

Albumin levels were unaffected by treatment during the study and, as can be expected, the albumin/globulin ratio was significantly decreased at 12 months in females at 1000 ppm.

Transient increases in mean serum chloride values for the 0, 100, 500, and 1000 ppm female groups at 12 months in comparison to controls are considered to be due to the slight lowering in control values at this time (12 months). These findings in serum chloride are not considered toxicologically significant.

Although there were statistically significant increases and decreases of mean values for brain, RBC and plasma cholinesterase, no toxicologically significant dose-related trends were observed and most individual values of treated groups were within the range of control values.

There were no compound-related urinalyses findings at each of the measured intervals in male or female rats.

With respect to gross necropsy findings, there were no compound-related gross necropsy observations in male rats. In female rats, the incidences of focal, tan

22

Summary of Serum Total Protein (g/dl) Mean Values for Rats Given SC-0224 in Diet

	Dosage Group (ppm)	Pretest n = 20	6 Months n = 10	12 Months n = 10	18 Months n = 10	24 Months n = 10
Males	Control	6.4 (0.3)		6.9 (0.2)		6.1 (0.5)[a]
	0		7.2 (0.4)	6.8 (0.3)	6.5 (0.4)	6.1 (0.4)[a]
	100		7.2 (0.4)	6.9 (0.3)	6.6 (0.4)	6.2 (0.4)[a]
	500		7.1 (0.3)	6.7 (0.3)	6.3 (0.3)	6.1 (0.4)
	1000		7.0 (0.3)	6.5 (0.5)	6.4 (0.3)	6.0 (0.5)
Females	Control	6.4 (0.2)		7.3 (0.4)		6.9 (0.2)
	0		7.6 (0.5)	7.4 (0.2)	7.2 (0.5)	6.6 (0.4)[b]
	100		7.7 (0.5)	7.5 (0.4)	6.9 (0.5)	6.8 (0.3)
	500		7.6 (0.6)	7.9 (0.5)*	7.0 (0.3)	7.0 (0.3)
	1000		7.5 (0.5)	8.0 (0.6)**	6.8 (0.4)	6.6 (0.6)[c]

* Significantly different from control; $p < 0.05$
** Significantly different from control; $p < 0.01$
() Standard deviation
a n = 9
b n = 7
c n = 8

23

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Summary of Serum Globulin (g/dl) Mean Values for Rats Given SC-0224 in Diet

	Dosage Group (ppm)	Pretest n = 20	6 Months n = 10	12 Months n = 10	18 Months n = 10	24 Months n = 10
Males	Control	2.8 (0.2)		3.3 (0.3)		3.3 (0.2)[a]
	0		3.4 (0.3)	3.2 (0.4)	3.4 (0.3)	3.3 (0.4)[a]
	100		3.4 (0.4)	3.4 (0.4)	3.5 (0.5)	3.4 (0.4)[a]
	500		3.4 (0.3)	3.2 (0.2)	3.2 (0.2)	3.2 (0.4)
	1000		3.3 (0.4)	2.9 (0.2)	3.3 (0.2)	3.2 (0.4)
Females	Control	2.5 (0.2)		2.9 (0.5)		3.3 (0.4)
	0		2.9 (0.5)	3.0 (0.2)	3.3 (0.3)	3.2 (0.4)[b]
	100		3.1 (0.5)[a]	3.0 (0.4)	3.0 (0.4)	3.1 (0.5)
	500		3.0 (0.5)	3.4 (0.2)*	2.9 (0.2)*	2.9 (0.3)
	1000		3.0 (0.5)	3.5 (0.4)**	2.9 (0.2)*	3.0 (0.5)[c]

* Significantly different from control; $p < 0.05$
** Significantly different from control; $p < 0.01$
() Standard deviation
a n = 9
b n = 7
c n = 8

discoloration of the medial lobe of the liver showed the following incidences:

Dose (ppm)	Control	0	100	500	1000
No. Examined	60	80	80	80	90
Liver					
Tan focal discoloration	5	3	2	4	13
Percent response	8	4	3	5	14

The increased incidence at 1000 ppm in female rats is not considered compound-related because there is no other evidence in this study suggesting that the liver is a target organ. All other indicators of potential liver toxicity (with the possible exception of decreased lactate dehydrogenase) were essentially negative.

Organ weights showed occasionally slight decreases or increases in treated female animals in comparison to controls, but none of the differences at any interval (6, 12, 18, or 24 months) were statistically significant or compound related.

In male rats at 6 months, at 500 ppm, there was a significant increase in testes weight (left and right weighed together) in absolute weight (161% of control and relative to brain weight 116% of control), but not relative to body weight (114% of control). Since there was no significant effect at 1000 ppm, the finding at 500 ppm was not dose-related and is not considered toxicologically significant.

At 12 months in comparison to controls, absolute liver weight was decreased as well as absolute kidney weight (both left and right) at 1000 ppm in males. These decreased organ weights at 1000 ppm also were present as decreased relative to brain weight (88% of control for left kidney, 86% of control for right kidney, and 79% of control for liver) but not relative to body weight (100% of control for left kidney, 97% of control for right kidney, and 89% of control for liver). These decreased organ weights probably reflect the decreased body weight at 1000 ppm and are not likely to be a significant toxic effect at 12 months.

Also noted at 12 months in males were an increased (relative to body weight) weight of the right testes at 500 ppm. This increase was not dose-related and was not reflected as an increase relative to brain weight or in absolute testes weight at 12 months and is not considered compound related. There were no organ weight effects in males at 18 months. At 24 months, the absolute brain weight of the 0, 500, and 1000 ppm male groups were all increased (105% of control for each group). In comparison to relative body weight, the increases were not statistically significant and are not considered compound related.

Evaluation of individual pathology sheets for control and treated animals (Appendix N; Volume 7 of report) did not give a clear indication that tissue masses that were identified grossly both antemortem and postmortem were examined microscopically. The tissue masses in clinical observations (Appendix I) and gross necropsy observations (Appendix L) were not clearly presented in the histopathology report (Appendix N) as being histologically examined. This deficiency has to be resolved by the registrant.

With respect to non-neoplastic histological lesions in male rats, chronic inflammation of the larynx and chronic inflammation of the nasopharynx were compound related at 1000 ppm.

Larynx (Males)

Dose (ppm)	Control	0	100	500	1000
No. Examined	60	80	79	78	90
Chronic Inflammation	13	20	9	16	34
Percent response	22	25	11	21	38

The grades of the lesion were comparable among groups. The most frequent grade was minimal.

The NOEL for chronic inflammation of the larynx is 500 ppm.

26

Nasopharynx (Males)

Dose (ppm)	Control	0	100	500	1000
No. Examined	60	80	80	80	90
Chronic Inflammation	6	11	6	4	20
Percent response	10	14	8	5	22

The grade of the lesions was comparable among groups. The most frequent grade was minimal. The NOEL for chronic inflammation of the nasopharynx is 500 ppm.

In female rats at the 6-, 12-, and 18-month interim sacrifices, there was an increased incidence of cardiomyopathy in the 100 and 500 ppm dose groups. The incidence was 3 percent, 23 percent, 17 percent, and 10 percent for the 0 (vehicle control), 100, 500, and 1000 ppm groups, respectively.

At 24 months, the incidence of cardiomyopathy was comparable among groups. The incidences were 81 percent, 93 percent, 72 percent, 100 percent, and 100 percent for the control, 0, 100, 500, and 1000 ppm groups, respectively.

For all female rats on study, the incidence of cardiomyopathy was as shown below:

Heart (Females)

Dose (ppm)	Control	0	100	500	1000
No. Examined	60	80	80	80	90
Cardiomyopathy	34	33	44	39	36
Percent response	57	41	55	49	40

The grade of the lesion was comparable among groups. The most frequent grade was minimal. Due to the decreased incidence of cardiomyopathy at the high-dose (1000 ppm) in the interim sacrifice and the similar frequency at the 24-month sacrifice and in all female rats examined, the increased incidences in the interim sacrifices at 100 and 500 ppm are not considered compound-related.

The incidences and grades of the non-neoplastic lesions for other organs of male and female rats were comparable between groups.

There were no compound-related benign or malignant tumors in male and female rats. Additionally, there was no decrease in latency in any tumor for either sex of rats. The most frequently observed neoplasms were of the pituitary, mammary gland, and adrenals. The incidences of the most commonly found tumors are shown below:

Pituitary - Adenomas/Carcinomas

	Male					Female				
Dose (ppm)	Control	0	100	500	1000	Control	0	100	500	1000
No. examined	60	79	80	77	90	60	78	80	80	88
No. of tumor bearing animals	44	41	43	34	47	52	56	57	55	58
Percent	73%	52%	54%	44%	50%	87%	72%	71%	69%	66%

Female Mammary Gland - Adenomas/Carcinomas

Dose (ppm)	Control	0	100	500	1000
No. examined	59	80	80	80	90
No. of tumor bearing animals	28	29	33	33	22
Percent	48%	36%	41%	41%	24%

Adrenal Pheochromocytoma - Benign and Malignant

Dose (ppm)	Control	0	100	500	1000
No. examined (both sexes)	60	80	80	80	90
No. of males with tumor	18	18	13	14	13
No. of females with tumor	5	6	3	2	3

Discussion

Mean body weights of 1000 ppm male rats were decreased through the initial 49 weeks of the study by 8.3 to 10.1 percent. Mean body weights of 1000 ppm female rats were decreased through the initial 75 weeks by 8.2 to 9.4 percent. The body weight decreases for high-dose (1000 ppm) male and female rats during the study is considered as evidence of an MTD.

At study termination, the number of survivors in each group of male rats was 17, 18, 12, 19, and 23 for control, 0, 100, 500, and 1000 ppm, respectively. For females at study termination, the number of survivors in each group was 16, 15, 25, 15, and 16 for control, 0, 100, 500, and 1000 ppm, respectively.

Lactate dehydrogenase levels in male and female rats at 6 and 12 months were decreased in a dose-related manner. The NOEL for these effects was 100 ppm. Evaluation of individual pathology sheets for control and treated animals (Appendix N) did not give a clear indication that tissue masses that were identified grossly in the antemortem and postmortem examination were examined microscopically.

The tissue masses listed in Appendix I (clinical observations) and Appendix L (necropsy observations) were not clearly identified in the histopathology sheets (Appendix N) as being histologically examined. This deficiency has to be addressed by the registrant.

Histologically, at 1000 ppm, there was an increased incidence of chronic inflammation of the larynx and nasopharynx in males.

There were no compound-related benign or malignant tumors in male or female rats. Additionally, there was no decrease in latency in any tumor for either sex of rats. However, these are tentative conclusions since the study is Core-Supplementary.

29

R:16869:Dykstra:C.Disk:KENCO:12/6/87:EE:SG:VO:CB
R:16892:Dykstra:C.Disk:KENCO:12/22/87:CB:VO:CB